Dichloroacetate (DCA) Summary for Intravenous and Oral Supplementation

As used at Anderson Medical Specialty Associates and in the Bastyr University Clinical Research Center (BCRC).

Paul S. Anderson: Last Update 01-12-2014

Overview:

DCA is a relatively small molecule, which has been used as treatment for lactic acidosis. It inhibits lactate formation and releases pyruvate dehydrogenase kinase from negative regulation, thus promoting pyruvate entry into the TCA cycle (3). This increases oxygen consumption and reactive oxygen species (ROS) formation while glycolysis and lactate formation are repressed (3). Non-cancerous human cells prefer this aerobic pathway for energy formation via the electron transport chain (ETC) use. Cancerous cells experience the Warburg Effect where most glucose is converted to lactate regardless of oxygen availability (9). Forcing a cancerous cell into TCA / ETC use thereby increases ROS formation and oxygen consumption (6).

Mitochondrial Dynamics:

The mitochondrial membrane potential is different in normal versus cancerous cells. The cancer cell mitochondrial membrane is hyperpolarized making the cancer cell resistant to apoptosis (1). Although DCA depolarizes both normal and cancer cells (3) it leads to cancer cell apoptosis while sparing normal cells (1). This is likely due to the great difference between resting mitochondrial membrane potentials in cancerous and normal cells.

Activation of p53 (and others) may be essential for membrane potential changes that trigger apoptosis (7). DCA in GBM cells has shown an ability to increase mitochondrial ROS (mROS) sensitive p53 activity, leading likely to the ant proliferative and pro-apoptotic effects of DCA on GBM (1). DCA was shown to have these effects in vitro and in vivo without affecting normal mitochondria or tissues (1). Increased mROS is more likely to induce apoptosis than cytosolic ROS increase (8).

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Functional p53 (and others) are necessary and may be essential for membrane potential changes that trigger apoptosis (7). DCA in glioblastoma multiforme cells (GBM) has shown an ability to increase mitochondrial ROS (mROS) sensitive p53 activity, leading likely to the anti-proliferative and pro-apoptotic effects of DCA on GBM (1). DCA has these effects in vitro and in vivo without affecting normal mitochondria or tissues (1). One source postulates that increased mROS is more likely to induce apoptosis than cytosolic ROS increase (8).

Glutathione and DCA:

The tripeptide glutathione (GSH) has multiple direct and indirect interactions with DCA metabolism and its effects. It has been reported (2) that GSH is consumed in DCA metabolism. This may be due to the fact that GSH is a cofactor for 4-maleylacetoacetate (MAAI) which is depleted during DCA metabolism. Decreased MAAI is associated with one potential cause of DCA toxicity (2). Additionally, NAC and ascorbate have been shown to enhance the activity of DCA (3).

As DCA and GSH have an apparent supportive relationship, yet GSH and oxidative therapies may have a non-supportive relationship if co-administered, it may be reasonable to assume that properly timed administration and restriction of GSH with the DCA would be reasonable. And while this idea is speculative a potentially reasonable recommendation would be to avoid GSH on treatment days when DCA is used concurrently with oxidative therapies, but allow GSH on treatment days when DCA is not given concurrently with oxidative therapies.

Cancers Targeted:

GBM are targeted due to their reliance on glucose metabolism, as well as the ability of DCA to cross the blood brain barrier (1). Other cancer cell types which have shown sensitivity are breast, prostate, colorectal, pancreatic and endometrial cancers (3).

Protocols Reported:

IV Administration of the DCA if possible in the early weeks of treatment, and in anyone with oral intolerance of the drug, ideally two non-consecutive days per week.

- 50-80 mg/kg IV DCA (10) plus support nutrients

If adding to a high dose IV ascorbate approach a reasonable protocol would be to alternate concomitant use of DCA plus High Dose IV Vitamin C, and DCA plus glutathione support (two separate IV's).

- IV-1 DCA plus Support Nutrients, with IV GSH
- IV-2 DCA plus high dose IVC

The use of DCA orally for long term therapy (if tolerated).

- 15-20 mg/kg Oral dose (10) cycle14 days on and 7 days off.

Appropriate neurological support:

- Lipoic Acid Mineral Complex (Poly MVA 20-40 mL) – or -
- B-1 100 mg BID-TID (or Benfotiamine 80 mg BID), glutathione precursors (ALA 300 mg BID) or IV administration of glutathione, Acetyl-l-Carnitine 500 mg BID-TID. (10)

The addition of a Ketogenic Diet is reasonable, as both DCA and the ketogenic diet take advantage of the Warburg effect of neoplastic metabolism. Recommend either a full (20 gram carbohydrate) or modified (50 gram carbohydrate) ketogenic diet plan.

Other protocols of note:

Michelakis, et.al. used an oral dosing protocol as follows: (1)

12.5 mg/kg PO X 1 month

Then 25 mg/kg PO

Decreased dosing by 50% if any signs of toxicity were noted.

Lemmo reported a combination IV and PO therapy in a small case series as follows: (5)

IV Loading dose X two weeks:

100 mL Normal Saline; DCA 1 – 3 Grams; 1mL B-Complex 100; 1mg B-12; 100mg B-6; 250mg B-5; 100mg B-1 (Infused over 30 – 60 minutes.)

Oral Protocol:

500mg BID, PO dissolved in juice for 1-3 weeks – increasing to 1500mg BID. If side effects exist decrease dose to 500 – 1000 mg BID PO.

Side effects and Toxicity:

The most common toxicity is a dose dependent reversible peripheral neuropathy. Other reactions appear to be mediated by a slowing of glutathione activity via the GSTz pathway: "From the Abstract: Dichloroacetate (DCA) inhibits its own metabolism and is converted to glyoxylate by glutathione S-transferase zeta (GSTz). … Moreover, DCA-induced inhibition of tyrosine catabolism may account for the toxicity of this xenobiotic in humans and other species." (11) As clinically most toxicity effects appear to be mitigated either by slowing infusion, adding glutathione and nutrient support or both the use of such additional measures is indicated.

Research Directions:

It would be reasonable to consider the following in implementing DCA as a cancer therapy:

- DCA appears synergistic with both oxidizing therapies, low dose ascorbate as well as glutathione supportive therapies – although oxidants and glutathione therapies are relative contraindications for one another at the same time.
- Glutathione is used in the metabolism of DCA and likely is preventive against DCA side effects.
- IV Dosing would be preferential in early treatment as a loading dose, as well as avoiding the oral side effects of DCA.
- Oral side effects appear to be limited to the aforementioned neuropathy and (more commonly) GI upset.
- DCA is likely to be effective in more than CNS tumors.

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